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The return of the bubonic plague?

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Abstract

The Plague has returned to be in the center of discussions between the centers of infectious diseases, since in Mongolia were recently reported the appearance and death of two probable cases of this disease, which has caused devastating pandemics for the human species, such as the Black Death in the Middle Ages. The bubonic plague is an infection caused by the microorganism Yersinia pestis, which is spread in the human body by lymphatic route from its sites of inoculation, causing an intense inflammatory picture characterized by fever> 38 ° C, malaise, myalgias, dizziness, vomiting and pain, caused by the inflammation of the regional lymph nodes (buboes), which can lead to septic shock and cause the death of the patient. The report of these two cases, considers important to maintain control and prevent an epidemic outbreak on time, however it becomes necessary to make a literature review about this disease, to remember its clinical manifestations, diagnosis, and treatment.

Keywords: *Yersinia pestis*; Plague; Review

¿El regreso de la peste bubónica?

Resumen

También llamada la Peste o Plaga (Plague en Ingles), ha vuelto a estar en el centro de discusiones entre los centros de enfermedades infecciosas, dado que en Mongolia se reportaron recientemente la aparición y fallecimiento de dos casos probables de esta enfermedad, que ha ocasionado las pandemias devastadoras para la especie humana, como la Peste Negra en el medievo. La peste bubónica es una infección causada por el microorganismo Yersinia pestis, que se disemina en el organismo humano por vía linfática desde sus sitios de inoculación, provocando un cuadro inflamatorio intenso caracterizado por fiebre >38 °C, malestar general, mialgias, mareos, vómitos y dolor, ocasionado la inflamación de los ganglios regionales (bubones), lo que puede desembocar en un choque séptico y ocasionar la muerte del paciente. El reporte de estos dos casos, estima importancia para poder mantener el control y evitar un brote epidémico de forma oportuna, sin embargo, se vuelve necesario el realizar una revisión bibliográfica acerca de esta enfermedad, con la finalidad de recordar sus manifestaciones clínicas, diagnóstico y tratamiento.

Palabras clave: *Yersinia pestis; Peste; Revisión*

Abstrato

A Peste voltou a estar no centro das discussões entre os centros de doenças infecciosas, já que na Mongólia foram recentemente relatados o aparecimento e a morte de dois casos prováveis dessa doença, o que causou pandemias devastadoras para as espécies humanas, como o Black. Morte na Idade Média. A peste bubônica é uma infecção causada pelo microrganismo Yersinia pestis, que se espalha no corpo humano por via linfática a partir de seus locais de inoculação, causando intenso quadro inflamatório caracterizado por febre> 38 ° C, mal-estar, mialgias, tonturas, vômitos e dor causada pela inflamação dos gânglios linfáticos regionais (bolhas), que pode levar ao choque séptico e causar a morte do paciente. O relato desses dois casos, considera importante manter o controle e evitar um surto epidêmico a tempo, porém torna-se necessário fazer uma revisão da literatura sobre esta doença, para lembrar suas manifestações clínicas, diagnóstico e tratamento.

Palavras-chave: *Yersinia pestis; Praga; Revisão*

Introduction

The bubonic plague is a zoonosis that has accompanied the human species throughout history, being remembered so far by the outbreak in the middle ages as the "black plague" or "the black death", which is estimated to decimate almost half of the population of Europe, arriving from Asia in 1346 via trade routes. [1-3]

Two new cases of plague reported in passengers of a commercial plane in Mongolia on May 1, 2019, after the intake of raw marmot kidney (since in some regions of Asia they believe it has medicinal properties), triggered the infection and subsequent death of the infected, in addition to the quarantine of the region. [4]

Given the high lethality of this disease close to 100% according to some authors, and having endemic foci in the Ecuadorian highlands, the importance of conducting a review about this entity. [1-5]

Development

Definition

Bubonic plague (plague) is an infectious disease caused by the microorganism *Yersinia pestis*, which predominantly infects small

rodents such as rats, mice and squirrels, with high mortality among them, and is transmitted to humans by a vector (infected flea); it is a member of the genus Yersinia, which is composed of 11 different species, of which 3 are considered pathogens of importance to humans (*Y. pestis*, *Y. enterocolitica*, and *Y. pseudotuberculosis*); the pest, bubonic plague or plague, is one of the infectious diseases of greatest impact on modern civilization, some authors point to it as one of the related causes of the collapse of the Roman Empire. [1, 5-8]

History & Epidemiology

It is a zoonotic infection that affects rodents, the disease in humans is incidental (as they do not contribute to the natural cycle of the disease), it is maintained worldwide by transmission of fleas among partially resistant rodents (enzootic or maintenance hosts), and occasionally it can spread to susceptible hosts (epizootic or amplifying), which can die in high numbers per epidemic. [5]

Episodes of pandemics have been recorded throughout history, as in 541 AD. named the plague of Justinian (Byzantine emperor), with subsequent outbreaks over 200 years; the second pandemic occurred from an outbreak in 1334 in China, and through the trade routes it spread to Constantinople and later to Europe, impacting 60% of the population of this region, being called the black death or great plague, decimated between 75 and 200 million people, for an estimated world population of 450 million; The last known pandemic was the "China Plague or Modern Plague" which is believed to have started around 1855-1860 in the province of Yunnan, and later spread to Hong Kong in 1894, from where it spread to the rest of the world reaching a number of 10 million deaths. [3, 5, 6]

Gracio & Gracio (2017) described in their study about the plague, 2 outbreaks that occurred in Angola, 200 cases (between 1973-1974 and 1975) where all the subjects were treated and only 11 died; between 2000 and 2009, in 16 countries around the world, 1612 deaths were reported in relation with this disease, being 95% of the reported cases of African origin. [5, 7]

Countries in Asia (such as Mongolia) are predominantly identified as natural or endemic foci of the disease, and in the Americas, areas such as central and southern Ecuador, northern and southeastern Peru, western and eastern Bolivia, and southeastern Brazil (image 1). [8]



Image 1. Distribution map of natural foci of bubonic plague in rodents (WHO plague map 2016). Note the central Ecuadorian highlands and northwestern Peru, referred to as *Y. pestis* endemic areas by the World Health Organization.

Microbiological aspects

Y. pestis is a cocobacillus, facultative anaerobic, fermenting, gram-negative, bipolar stained with Giemsa, Wrigth or Wayson technique, grows in media such as blood agar and MacConkie, and can be incorrectly detected by automated systems; 3 subspecies of *Y. pestis* have been described in the literature, *Antiqua*, *Mediavalis* and *Orientalis*, and a fourth variety or subspecies (*Microtus*) has been proposed; *"Genetic studies indicate that Y. pestis evolved from the enteric pathogen Y. pseudotuberculosis shortly before the first known human plague pandemics, through the transmission of two unique plasmids and the inactivation of genes necessary for survival in the mammalian gut"*. [5]

The transmission mechanism classically proposed describes that the microorganisms reach the human being through the bite of an infected flea, colonizing the intestine of the same, replicating and producing the blockade of the flea (blocked flea model), this hungry, feeding aggressively, regurgitating the bacteria in the wound of the bite in each attempt to feed, it has been established that the minimum inoculum to infect mammals is 10 microorganisms subcutaneously; In humans, the spread of the microorganism

(which is facilitated by the bacterium's J protein, which kills macrophages, facilitating the spread to nearby areas) is carried out by lymphatic transport to the regional nodes of the inoculation site, producing an intense inflammatory reaction, which causes the bubo; after the spread, necrotic foci containing *Y. pestis* are formed and increased. extracellular pestis, this stage is facilitated by the deterioration of the function of local immune cells; it has been mentioned that transmission between humans occurs mainly through aerosol droplets. [1, 3, 5-9]

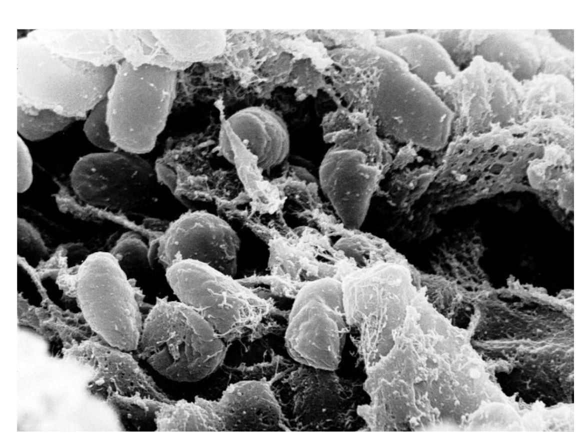


Image 2. Electronic micrograph representing a mass of *Yersinia pestis* bacteria (causal agent of bubonic plague) in the anterior intestine of the vector (fleas). Public domain image, Rocky Mountain Laboratories, NIAID, NIH.

Clinical manifestations

Bacteremia is common and can cause sepsis, pneumonia and hemorrhagic lesions in various organs; in the absence of therapy, plague sepsis and endotoxemia lead to the release of pro-inflammatory mediators, the resulting systemic inflammatory response syndrome can lead to disseminated intravascular coagulation, bleeding, organ failure and shock. [1, 5]

The most common form of manifestation is bubonic plague, which appears after an incubation period that is established at an interval of 2 to 8 days. The clinical picture is characterized by the appearance of symptoms such as fever >38°C, chills, headache, general malaise, myalgias, dizziness, vomiting and pain with gradual increase in intensity as a result of progressive lymphadenitis in regional nodes near the site of inoculation, which are enlarged, swollen or inflamed (buboes), with fluctuating consistency, with a hard center. Other forms of presentation are primary septicemia that is not preceded by lymphadenopathy and pneumonic plague. [1]

The septicemic form is still discussed today since it represents 10-25% of cases. Its diagnosis is established from the isolation of the microorganism from blood cultures, and it is associated with severe clinical picture characterized by hypotension, acute respiratory distress, intravascular coagulopathy (septic shock), with consequent deterioration of the patient's condition, and hemorrhagic, cardiovascular, neurological and renal complications; it is in this form of presentation, the fascie pestica can be observed (anxiety, pain, extreme weakness and resignation), and its mortality exceeds 90%. [5-6, 10]

Pneumonic plague is the most severe and lethal form of presentation, the primary forms (which are usually more severe than the secondary form) are believed to be produced by inhalation of inter-human or burrowing dust contaminated with Yersinia pestis, while the secondary form is the result of the hematic or lymphatic spread, from the bubo or septicemic form; the evolution of pneumonic plague is rapidly progressive and usually fatal within 24-72 hours in more than 90% of cases in the absence of treatment, its clinical manifestations may be coughing, expectoration, chest pain, and sometimes hemoptysis and dyspnea. [3, 10]

Patients with fever and painful lymphadenopathy should be questioned about travel to endemic areas, contact with animals or rodents with vectors, within 10 days prior should lead to the differential diagnosis. [1, 5-6, 9-17]

Diagnosis

The diagnosis is established by isolating the organism in culture or by means of serological tests; microbiology personnel must be informed of any suspicious samples so that they can take appropriate precautions to prevent the acquisition of infection in the laboratory; positive results in blood cultures range from 27-96%; aspiration of the bubo after injection with saline to obtain the sample is the most appropriate method for making the diagnosis of bubonic plague. [1, 3, 5-6, 9-17]

Therapeutics

Based on non-randomized studies, the treatment of choice has long been streptomycin, gentamicin is equally effective in comparative studies [11]; although aminoglycosides are traditionally considered the most effective treatment, fluoroquinolones or cyclines are currently recommended in France [3]; streptomycin and gentamicin are recommended for treatment in both children and adults, including immunocompromised patients and pregnant women [12]; therapy is recommended parenterally for at least 10

days, and alternatively fluoroquinolones, doxycycline, tetracycline, TMP/SMX and chloramphenicol [11].

Streptomycin was considered the drug of choice for the treatment of plague, starting with studies in 1940 and 1950; it is not currently available in many parts of the world, however, the recommended dose is 30 mg/kg day, in intramuscular application, up to a total dose of 2 g/day; Alternative antibiotic agents include gentamicin, which is safer than streptomycin in pregnant women and children; doxycycline (loading dose on day 1, 200 mg orally [VO] or intravenously [IV] every 12 hours; followed by 100 mg every 12 hours) and tetracycline (2 g/day, divided into 4 doses) are acceptable alternative regimens for patients who cannot tolerate aminoglycosides; levofloxacin (500 mg IV every 24 hours for 10 days), ciprofloxacin and moxifloxacin, have been shown to be effective against plague in animal studies, however their use is reserved for patients who cannot tolerate tetracyclines or aminoglycosides; Chloramphenicol (25-30 mg/kg with a maximum of 2 g as loading dose, followed by 50-60 mg/kg day with a maximum of 4 g/day, divided into 4 doses, reducing to 25-30 mg/kg per day, with the clinical improvement of the patient) and trimethoprim-sulfamethoxazole have been used as a scheme for the treatment of plague, however with the second the clinical response may be late or incomplete, hence it is not recommended as a first line of treatment. [5, 6, 9-17]

The optimal duration of antimicrobial therapy for plague is uncertain; regimens are usually administered at 7-14 day intervals and at least a few days after clinical signs and symptoms of infection have resolved, it is recommended that patients suspected of having some form of plague should receive droplet precautions, until the pneumonic form has been ruled out, until sputum cultures are negative, and until at least 48 hours of effective antimicrobial therapy have been administered. [5, 6, 9, -17]

In case of suspected outbreaks or bioterrorist attacks, the recommended oral presentations of the drugs doxycycline and ciprofloxacin should be used for the treatment of plague in both children and adults 12. Both the rapid diagnosis will allow the initiation of treatment in a timely manner, which can reduce the mortality rate (TM) associated with plague in its various forms, being the reduction of the pulmonary (TM 100%) to 50-60%, bubonic (TM 40-60%) is reduced to less than 10% and in septicemic plague (TM 90-99%) to 5-50%. [6, 7, 11-17]

Conclusions

The plague continues to represent a serious threat to the human race, is considered a re-emerging disease according to the WHO, its appearance is usually episodic and in outbreaks; Ecuador has areas of endemic foci, while in Peru is considered an endemic disease per se, its diagnosis and timely treatment, contribute to reducing the mortality of cases, which in most forms, ranging from 50% to over 90%.

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